UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/408,905	09/29/1999	KENNETH WALSH	S1237/7011/E	4597

7590 05/17/2006

ELIZABETH R PLUMER
WOLF GREENFIELD & SACKS P C
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/408,905	WALSH, KENNETH	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 39-58* is/are pending in the application.

4a) Of the above claim(s) *51-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 39-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Walsh, Kenneth

DETAILED ACTION

The examiner of the application has changed. This case has now been transferred as of 5/04/2006. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Brandon Fetterolf, Group Art Unit 1642.

Response to the Amendment

The Amendment filed on 03/06/2006 in response to the previous Non-Final Office Action (11/03/2005) is acknowledged and has been entered.

Claims 1-5 and new claims 39-58 are currently pending.

New claims 51-58, as specifically drawn to a method of treating myocardial infarction comprising: administering to a subject in need of such treatment an Akt polypeptide in an amount effective to inhibit cardiac tissue necrosis in the subject, wherein the Akt polypeptide shares at least 98% amino acid identity with SEQ ID NO: 2 are withdrawn from consideration because the claims are drawn to subject matter which has been previously withdrawn from consideration as being drawn to a non-elected invention.

Claim 1-5 and 39-50 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claims 1-6 remain rejected and new claims 39-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of treating a subject for myocardial infarction, comprising the step of: administering to the subject in need of such treatment a composition comprising a replication-defective adenovirus comprising a polynucleotide, wherein said composition is administered acutely

into the apical and anterolateral free wall of the heart, wherein said polynucleotide comprises a nucleotide sequence that encodes an Akt polypeptide, operatively linked to a promoter to promote expression of the Akt polypeptide in cardiomyocytes, wherein the Akt polypeptide comprises: the amino acid sequence of SEQ ID NO: 2.

--does not reasonably provide enablement for the broadly claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practive the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method for treating myocardial infarction comprising administering to a subject in need of such treatment an Akt molecule in an amount effective to inhibit cardiac tissue necrosis.

The specification teaches (page 7) that an "Akt" molecule includes both Akt nucleic acids and Akt polypeptides. Thus, the claims are broadly inclusive of treating myocardial infarctions via gene therapy or by simply administering any Akt polypeptide or nucleic acid in any manner.

However, one cannot extrapolate the teachings of the specification to the scope of the claims because applicant has not enabled all of these types of modified Akt proteins and nucleic acids for the treatment of myocardial infarctions. Those of skill in the art of gene therapy recognize that such therapy is highly unpredictable. For example, Crystal, R. (Science, Vol. 270, 1995, pages 404-410) teaches (page 409) that there are many obstacles to successful human gene therapy including inconsistent results, studies in experimental animals are not predictive in humans, and vector production problems. Further, Anderson, W. (Nature, 1998, Vol. 392, pages 25-30) teaches

that although gene therapy as a treatment for disease holds great promise, progress in developing effective clinical protocols has been slow. Anderson adds that the problem lies in the development of safe and efficient gene-delivery systems. And, although the specification teaches that adenoviral vectors were used in the delivery, the claims are not limited to any specific delivery protocol, vector system, or delivery locale. Reasonable correlation must exist between the scope of the claims and scope of enablement. Thus, as written, and according to the art of record, it would be unpredictable that the claimed method would function as broadly claimed.

In response to this rejection, Applicants assert that the specification need not necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of prior art and routine experimentation can often fill gaps interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments. See Chiron Corp. v. Genetech, Inc., 363 F.3d 1247. For example, Applicants submit that the knowledge of a person skilled in the art and routine experimentation can fill the gap of delivering every species of the Akt (nucleic acid and polypeptide) into a subject to treat myocardial infarction. Applicants contend that the specification teaches that Akt is a serine-theonine kinase and can phosphorylate proteins involved in apoptotic cell death, such as *Bad*, resulting in the inactivation of these proteins and cell survival. Based on the biological function of Akt, Applicants submit that either an Akt polypeptide or an Akt nucleic acid that encodes an Akt polypeptide in cells can be used to inhibit apoptotic cell-death, in particular, to treat conditions such as myocardial infarction. Applicants further submit that it is well known in the art that proteins, which are highly homologous at the amino acid level, e.g., sharing >95% amino acid identity, are very likely to have the same biological function. Therefore, Applicants argue that it is predictable that an Akt polypeptide cited in the claims would have the same biological function as human Akt, e.g., being a serine-theronin kinase and capable of inhibiting apoptotic cell death, because the speciation teaches that mouse Akt is 90% homologous to human Akt at the nucleic acid level and 98% homologous at the amino acid level. Applicants further submit that it is predictable that an Akt nucleic acid encoding an Akt polypeptide as recited in the pending claims can be used to treat myocardial infarction in a subject in need. Moreover, Applicants assert that the Examiner's interpretation of the claimed invention represents just a preferred embodiment of the invention and not the claimed invention as a whole. For example, Applicants assert that the claimed method is not just limited to the use of "a composition

comprising a replication-defective adenovirus comprising a polynucleotide" as stated in the OA, pages 4-5, but includes both an Akt nucleic acid and an Akt polypeptide can be used in the method of treating myocardial infarction (specification, page 2, lines 16-22 and 31-32). Therefore, Applicants contend that since an Akt polypeptide is the ultimate factor having the therapeutic effect, a person skilled in the art would recognize that direct administration of an Akt polypeptide would have the same effect as administration of a DNA construct capable of directing expression of an Akt polypeptide. Applicants further contend that the claimed method is also not limited to "acute administration into the apical and anterolateral free wall of the heart because a person skilled in the art would know that any method available in the prior art to deliver either nucleic acids or polypeptides to a tissue would also be applicable to the claimed invention. Also, Applicants assert that the claims are not limited to any specific delivery protocol, vector system or delivery locale. In addition, Applicants argue that neither Crystal nor Anderson, two references cited by the examiner to show that the lack of safe and efficient gene-delivery system rendered the technology of gene therapy unpredictable, denies the effect of transferring genes into the human body and then evoking expected biological responses. Moreover, Applicants assert that while Crystal and Anderson point out that a challenge of gene therapy is the development of "safe and efficient gene-delivery systems," safety and efficiency are not the relevant standard for enablement under 35 U.S.C. 112, first paragraph. For example, Applicants point out that MPEP 2164.01 (C) makes it clear that "the applicants need not demonstrate that the invention is completely safe." In fact, Applicants argue that it is within the domain of concern of the Food and Drug Administration, not the Patent Office, to determine whether a pharmaceutical composition or treatment is safe and effective when applied in human clinical use. In other words, Applicants submit that matters of safety and efficiency, being outside the enablement standard as the law requires, thus should not pose a bar to patentability. See In re Brana, 51 F. 3d 1560 (Fed. Cir. 1995).

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that the specification need not necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of prior art and routine experimentation can often fill gaps interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, the Examiner acknowledges and agrees with Applicants assertion that the specification need not describe how to make and use every possible

variant of the claimed invention. However, the Examiner recognizes that while Applicant's contend that the knowledge of a person skilled in the art and routine experimentation can fill the gap of delivering every species of the Akt (nucleic acid and polypeptide) into a subject to treat myocardial infarction, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. (emphasis added) For example, Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teach that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82). Regarding Applicants contention that it is predictable that the Akt polypeptide encoded by the nucleic acid cited in the claims and human Akt would have the same biological function based on their high sequence homology, the Examiner acknowledges and concedes that in some instances homology between two polypeptides can predict biological function. However, the Examiner recognizes that while the ultimate factor having the therapeutic effect is the Akt polypeptide, the claims under consideration are drawn to administration of a nucleic acid, e.g., gene therapy, and not to the administration of the polypeptide. In the instant case, there are several reviews in the art which show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, have created technical barriers to the practice of gene therapy methods. For example, Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that

"many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1). In response to Applicants assertion that the claimed invention is not just limited to the preferred embodiments, the Examiner agrees that the claims encompass not just the preferred embodiments, but also the use of any delivery mechanism available in the prior art and any delivery protocol, vector system or delivery locale. However, the Examiner recognizes that while the specification, as well as Applicants arguments, contemplate the use of both an Akt nucleic acid and polypeptide, any delivery mechanism available in the prior art and any delivery protocol, vector system or delivery locale, the specification is not enabled for any Akt nucleic acid, any delivery mechanism or any delivery protocol in view of (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art as set forth above and in the previous office action. Regarding Applicants assertion that the safety and efficiency concerns of Crystal and Anderson are not the relevant standard for enablement under 35 USC 112, first paragraph, the Examiner agrees with Applicants statement that it is within the domain of the Food and Drug Administration, and not the Patent office, to determine whether a pharmaceutical composition or treatment is safe and effective when applied to human trials. However, the Examiner recognizes that while Applicants have focused on the relationship between gene therapy and the development of a safe and efficient gene-delivery system from a clinical standpoint, it is apparent that those of skill in the art recognize the importance of a suitable gene delivery system. As stated above, Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3.

Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Thus, the art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Therefore, claims 1-6 remain rejected and new claims 39-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of treating a subject for myocardial infarction, comprising the step of: administering to the subject in need of such treatment a composition comprising a replication-defective adenovirus comprising a polynucleotide, wherein said composition is administered acutely into the apical and anterolateral free wall of the heart, wherein said polynucleotide comprises a nucleotide sequence that encodes an Akt polypeptide, operatively linked to a promoter to promote expression of the Akt polypeptide in cardiomyocytes, wherein the Akt polypeptide comprises: the amino acid sequence of SEQ ID NO: 2.

--does not reasonably provide enablement for the broadly claimed invention.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER